C1

1. (Amended) A composition of matter comprising: 1) a solid support; and 2) a printed pattern comprising a self-assembled monolayer of linear peptides, wherein said peptides are bound [directly] to said solid support [through] by a bond between the solid support and a terminal amino acid [in a predetermined pattern].

C2

8. (Amended) The composition of matter according to Claim 6 wherein said terminal reactive group is in the [a functional group pendant from a] side chain, is the alpha amino group or the alpha carboxy group of the terminal amino acid of the peptide.

C3

12. (Amended) The composition of matter according to Claim 10 wherein said central linker comprises between [about] 2 to [about] 50 amino acids.

C4

16. (Amended) A composition of matter comprising: 1) a solid support; and 2) a printed pattern comprising a self-assembled monolayer of linear peptides, wherein said peptides are bound [directly] to said solid support [through] by a bond between the solid support and a terminal amino acid [in a predetermined pattern], the peptide further being characterized by the formula:

$$X\text{-}(CH_2)_n\text{-}CH(NH_2)CO(AA)_m\text{-}L$$

or

$$X\text{-}(CH_2)_n\text{-}CH(COOH)NH(AA)_m\text{-}L$$

wherein X is H, alkyl, alkoxy, alkylthio or dialkylamine, thiol, hydroxy, amino or carboxy;

C

AA is, independently, the same or different, naturally-occurring or non-naturally-occurring amino acid;
L is a group which binds specifically or non-specifically to a target;
n is zero or an integer between 1 to [about] 5; and
m is an integer of at least [about] 2.

18. (Amended) A method for manufacturing a composition of matter comprising: 1) a solid support; and 2) a printed pattern comprising a self-assembled monolayer of linear peptides, wherein said peptides are bound [directly] to said solid support [through] by a bond between the solid support and a terminal amino acid [in a predetermined pattern], said method comprising the steps:

(a) contacting an elastomeric stamp characterized by a relief of said [predetermined] pattern with a solution containing a compound which can react with said solid support;

(b) contacting said stamp with a surface of said solid support under conditions suitable for the reaction between said compound and said solid surface, wherein said compound reacts with said solid support at points of contact between said stamp and said solid support, corresponding to the relief of said [predetermined] pattern;

(c) removing said stamp; and

(d) contacting said solid support with a solution containing said linear peptides under conditions suitable for the reaction of said peptide and said solid support.

19. (Amended) A method for manufacturing a composition of matter comprising: 1) a solid support; and 2) a printed pattern comprising a self-assembled monolayer of linear peptides, wherein said peptides are bound [directly] to said solid support [through] by a bond between the solid support and a terminal amino acid [in a predetermined pattern], said method comprising the steps:

(a) contacting an elastomeric stamp characterized by a relief of said [predetermined] pattern with a solution containing said linear peptide;

(b) contacting said stamp with a surface of said solid support under conditions suitable for the reaction between said linear peptide and said solid surface, wherein said linear peptide reacts with said solid support at points of contact between said stamp and said solid support, corresponding to the [predetermined] pattern; and

(c) removing said stamp.

Reply Under 37 C.F.R. § 1,111

In view of the Appeal Brief filed by Applicants on February 28, 2000, the Examiner re-opened prosecution and issued an Office Action that was mailed on May 8, 2000. Applicants are responding herein to the Office under 37 C.F.R. § 1.111.

Claim Objection Due to Informalities

The Examiner objected to Claims 1, 16, 18 and 19 due to informalities (grammatical errors). The errors have been correct by amendment.

Rejection of Claim 19 Under 35 U.S.C § 112, First paragraph

The Examiner stated that while the specification was enabling for a monolayer of peptide bound in the relief pattern of a pre-printed substrate, the specification does not reasonably provide enablement for direct, microcontact printing of peptides. The Examiner then applied the analysis in *In re Wands* while analyzing the state of the prior art and predictability in the art. The Examiner stated that although self-assembled monolayer and even patterning of monolayers by microcontact printing was well known at the time of filing, there were only a few examples of different molecules used for patterning and no examples of direct microcontact printing of peptides. She asserted further that the interaction of the "inking" compound and the stamp is crucial to the formation of good patterns and is not predictable, as taught at the bottom of page 1218 of by Zhang *et al., Biomaterials 20:*1213 (1999). The Examiner also stated that if might be

necessary to use a special elastomer for the stamp and that it might be necessary to experiment to select a proper wetting solvent.

The subject specification provides extensive guidance on the direct microcontact printing of surfaces with peptides, for example, page 13 line 3 through page 15, line 3. Particular note is made of page 14, lines 25-33 and Figure 1. Despite an extensive analysis of the criteria provided in *In re Wands*, the Examiner provided only three reason why the specification is not enabling for Claim 19: 1) the passage on page 1218 of Zhang; 2) the alleged need for a special elastomer for the stamp; and 3) the alleged need to experiment to select a suitable wetting solvent. Applicants respectfully disagree and respond to each of these points below.

Zhang does <u>not</u> show that the specification is non-enabling with respect to Claim 19. In particular, Applicants note that Zhang discloses the direct patterning of a gold surface with the molecule EG_6SH (see Section 2.6 entitled Pattern Formation", on page 1216, which describes how the gold surface was printed with a pattern of EG_6SH). EG_6SH is <u>not</u> a peptide, but is rather the compound 11-mecaptoundec-1-yl-(ethylene glycol)$(OH(CH_2CH_2O)_6(CH_2)_{11}SH$ (see page 1214, right column, second full paragraph). Therefore, Zhang is no way shows that the direct microcontact printing of peptides would be problematic. Moreover, this description provides the same procedure for patterning peptides onto surfaces as is taught page 13 line 3 through page 15, line 3 of the subject application, but for oxidizing the stamp with oxygen plasma. The oxygen plasma treatment is also discussed on the bottom of page 1218 of Zhang, to which the Examiner referred in the Office Action. However, printing a pattern of a SAM (including peptide SAMs) onto a surface can be carried out without the oxygen plasma treatment, which merely provides a more precisely defined pattern. The enclosed Declaration under 37 C.F.R. § 1.132 of Shuguang Zhang, Ph.D. co-author of Zhang, *et al.* and co-inventor of the subject application supports for position. This Declaration states that the use of oxygen plasma is a later developed improvement which results in more sharply defined patterns. This Declaration also states that printed patterns of peptide SAMs can be obtained without oxygen plasma treatment, as described in the subject application. Further evidence can be provided, if requested.

With respect to the alleged need for a special elastomer for the stamp, the Examiner has not provided any reason why a special stamp would be needed and why the selection of a suitable

stamp would be difficult. With regard to a suitable wetting solvent, the selection of suitable solvents is generally routine for one of ordinary skill in the art. Again, no reason has been given why this would difficult. The burden is on the Examiner to establish a reasonable basis to question enablement:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367 , 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370. MPEP 2164.04

The Examiner has merely asserted that selecting suitable elastomers and wetting solvents would require undue experimentation, but has provided no reason or rationale to support this assertion. Therefore, the burden of showing lack of enablement has not been met.

In summation, the passage in Zhang cited in Office Action discloses an improvement of direct microcontact printing and does not show that the method is unpredictable. In addition, no evidence has been provided to show that unreasonable experimentation would be required to select suitable elastomers for the stamp and suitable setting solvents. Normally, the selection processes are routine. Withdrawal of the enablement rejection is therefore requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner made five rejections under 35 U.S.C. § 112, second paragraph, which are addressed below under separate subheadings.

A. The term "pre-determined" in Claims 1, 16, 18 and 19

The term "pre-determined" in Claims 1, 16, 18 and 19 was said to be indefinite because it allegedly is not defined by the claim and the specification allegedly does not provide a standard fo ascertaining the requisite degree. The Examiner reasoned that one of ordinary skill in the art would be reasonably appraised of the scope of the claims.

Applicants disagree that the claims are indefinite because of the term "pre-determined". However, to advance prosecution, these claims have been amended so that the pattern is required to be printed. "Print", *v.t.* is defined in the second edition of "Random House Webster's College Dictionary" as follows (page 1049 of the dictionary is included herewith as Exhibit A):

> **1.** to produce (a text, picture, etc.) by applying inked types, plates, blocks or the like, to paper or other material either by direct pressure or indirectly by offsetting an image onto an intermediate cylinder.
>
> **2.** to reproduce (a design or pattern) by engraving on a plate or block.

Page 12, lines 13-27 of the subject application provides further clarity as to the meaning of the term "printed". Thus, the pattern of the self-assembled monolayer that is bound to the surface of the solid support is printed, meaning the pattern can be reproducibly applied to other solid surfaces by engraving an image of the pattern onto another substrate. The pattern is therefore non-random and pre-determined, again meaning that it can be reliably reproduced.

For reasons provided above, the term "printed" in Claims 1, 16, 18 and 19 is definite. Withdrawal of the rejection is therefore requested.

B. The term "bound directly" in Claims 1, 16, 18 and 19

The Examiner stated that Claims 1, 16, 18 and 19 were unclear because "bound directly" appears to have two meanings: 1) the physical attachment of the peptide to the solid support with no intermediary compounds between the peptide and the solid support; and 2) attachment to a

solid support via a terminal amino acid (no additional functionality added to the peptide), whether or not an intermediary compound is present.

Applicants disagree that the claims are confusing because of the term "bound directly". However, to expedite prosecution, Claims 1, 16, 18 and 19 have been amended to recite that there is a bond between the solid support and the terminal amino acid. Withdrawal of the rejection is requested.

C. Claim 8

The Examiner stated that Claim 8 is indefinite because it is unclear it appears that a functional group can be pendant from a side chain or amino or carboxy group of a terminal amino acid and would therefore encompass modified amino acids. The Examiner also stated that is additional lack of clarity because of the term "bound directly", which the Examiner said could be interpreted to mean no additional functionality bound to the peptide. Claim 8 has been amended so that the peptide is attached to the solid support by a reactive functional group in the side chain. Withdrawal of the rejection is requested.

D. The recitation of "about 2 to about 50 amino acids" in Claim 12

The Examiner stated that Claim 12 is indefinite because of the term "about". Although Applicants disagree, Claim 12 has been amended to delete this term in order to advance prosecution.

E. The recitation "at least about 2" in Claim 16

The Examiner stated that Claim 16 is indefinite because of the term "at least about". Although Applicants disagree, Claim 12 has been amended to delete this term in order to advance prosecution.

F. Objection to Claim 17

Claim 17 has been cancelled. The rejection is now moot.

Rejection of Claims 1-3, 6, 8-11 and 17 Under 35 U.S.C. § 102(b) As Being Anticipated In View of Duschl *et al.*

The Examiner stated that Duschl *et al.* (hereinafter "Duschl") teaches "the fabrication of patterns with contrasting surface properties on gold substrates". She further stated that self-assembled monolayers are formed in a pattern having ordered areas where the peptide are and are not bound.

Applicant respectfully disagrees that the subject matter of Claims 1-3, 6, 8-11 and 17 are anticipated by Duschl. However, to more clearly define the invention, the claims have been amended so the composition comprises solid support and a self-assembled monolayer of linear peptides that is printed on the solid support in a pattern. "Print", *v.t.* is defined in the second edition of "Random House Webster's College Dictionary" as follows (page 1048 of the dictionary is included herewith as Exhibit A):

> **1.** to produce (a text, picture, etc.) by applying inked types, plates, blocks or the like, to paper or other material either by direct pressure or indirectly by offsetting an image onto an intermediate cylinder.
>
> **2.** to reproduce (a design or pattern) by engraving on a plate or block.

Thus, "printed pattern" means that the pattern can be reproducibly applied to other solid surfaces by an image that has been engraved onto another substrate. The pattern is therefore "non-random" Page 12, lines 13-27 further clarifies the meaning of the term "printed".

The patterned SAM disclosed by Duschl are not "printed" or "pre-determined". The SAMs in Duschl are formed by the following procedure:

> A mixture of palmitic acid and a thiolipid that is been spread on a water/air interface of a Langmuir trough to form a monolayer. This monolayer phase-separates on compression to give regularly distributed domains containing predominantly fatty acid. The size of the domains depends only on the self-organizing properties of the mixture and its manipulation on the water surface. The film is then transferred to a gold substrate where the thiolipids bind covalently to the support. The fatty acid is only physiosorbed of the gold surface and can be washed away. . . (paragraph bridging pages 1229-30).

Thus, the palmitic acid molecules, which have the hydrophilic carboxylic acid end group, associate and thereby separate from the hydrophobic thiolipids. As a result, the palmitic acid molecules and the thiolipid molecules each form their own domains at the air water interface. However, the number of domains formed and number of molecules which associate in each domain, i.e., the size and location of each domain, is unpredictable. The pattern which forms from this process is random, unpredictable and irreproducible and therefore cannot be "printed" or "pre-determined". The subject matter of these claims is therefore novel in view of Duschl. Withdrawal of the rejection is requested.

Rejection of Claims 1-3, 5 and 18 Under 35 U.S.C. § 102(b) As Being Anticipated In View of Lopez *et al.*

The Examiner stated that Lopez *et al* (hereinafter "Lopez") teaches a pattern of proteins adsorbed on a self-assembled monolayer (SAM). The proteins were said to be adsorbed to a monolayer of CH_3-terminated SAM as described on pages 10776-77. These monolayers were said to be patterned in a variety of way, most importantly, by the stamping method of the instant invention. The Examiner also referred to the bottom of page 8 in Applicants' Response, dated January 11, 1999. Applicants respectfully disagree with the rejection.

Claims 1-3, 5 and 18 are directed to a composition comprising a solid support and a SAM of peptides. These claims, as amended, require the peptides to be connected to the solid support by a bond between the terminal amino acid and the solid support. The subject matter of Claims 1-3, 5 and 18 differs from the composition taught in Lopez because the compositions in Lopez comprise SAMs of alkanethiols, not peptides as required by Claims 1-3, 5 and 18. The proteins in the compositions of Lopez are absorbed onto the SAMs, they do *not* form SAMs. For this reason alone, the subject matter of Claims 1-3, 5 and 18 is novel in view of Lopez.

The subject matter of Claims 1-3, 5 and 18 differ from the compositions disclosed in Lopez for at least one other reason. As note above, the claims, as amended, require that the peptide be bound to the solid support through a terminal amino acid. Therefore, the interaction between the peptide and the substrate is *specific* in the sense that the peptide is bound to the

substrate at one specifically defined part of the peptide. The subject matter of Claims 1-5 and 18 differ from the teachings of Lopez because peptides are *adsorbed* onto SAMs in Lopez. *Adsorbed* means that the interaction between the peptide and the SAM is *non-specific* in the sense the that the SAM has attractive interactions with multiple groups on peptide, rather than specifically at the terminal amino acid, as required by Claims 1-5 and 18.

Support for Applicants position that the "adsorbed proteins" proteins in Lopez interact non-specifically with the SAM is provided by Zhang *et al., Biomaterials 20:*1213 (1999) (hereinafter "Zhang"), which was cited by the Examiner in her rejection of Claim 19 under 35 U.S.C. § 112, first paragraph. See, for example, the following passage from the first full paragraph on page 1214:

> For example, photolithography has often been used to create these micropatterns, followed by the *adsorption of protein* and cells to the solid surface. Since *protein adsorption is largely dependent upon non-specific interactions* between the protein and the surface, these methods cannot orient the adsorbed protein to uniformly expose the desire ligands. (emphasis added).

Thus, Zhang teaches that adsorption of proteins onto SAMs results in non-specific interactions.

The teachings of Lopez are also consistent with there being non-specific interactions between the SAM and the proteins. Note that in the first paragraph on page 10774, Lopez refers to "SAMs formed by *chemisorption* of oligo(ethylene glycol)-terminated alkanethiols $(HS(CH_2)_m(OCH_2CH_2)_nOH$" and that such "SAMs "resist *adsorption* of a variety of proteins." Thus, it is clear that Lopez makes a distinction between *chemisorption* and *adsorption*. It is well established that oligo(ethylene glycol)-terminated alkanethiols such as $(HS(CH_2)_m(OCH_2CH_2)_nOH$ form a specific chemical bond between the thiol and the gold surface of the SAM. It is noted further that in Lopez that "adsorption" occurs between $SH(CH_2)_nCH_3$ functionalized SAMs and the proteins. The thiol group is *chemisorped* to the gold surface, allowing *adsorption* to occur between the alkane group and the protein. A specific interaction between the terminal amino acid group and the alkane group, as required by Claims 1-3, 5 and 18, is not possible, and the Examiner has not indicated how such a specific interaction could

form. Therefore, the subject matter of Claims 1-3, 5 and 18 is novel in view of the teachings of Lopez. Withdrawal of the rejection is requested.

Rejection of Claims 1-4 and 8-10 Under 35 U.S.C. § 102(b) As Anticipated by Knichel *et al*

The Examiner stated that Knichel *et al.* (hereinafter "Knichel") teaches a self-assembled monolayer (SAM) of peptides on a patterned substrate. The Examiner reasoned that the substrate is glass with gold electrodes patterned thereon and that the thiol-modified peptide adheres only to the gold coated portions of the substrate (i.e. the pattern is the pattern of the underlying gold electrode and the peptides are not bound to the uncoated glass portions). Applicants respectfully submit that the compositions disclosed by Knichel is not encompassed by Claims 1-4 and 8-10.

Claim 1 is directed to a composition which comprises a solid support and a pattern of a peptide SAM printed thereon. Claim 1 requires: 1) that the peptide SAM *be printed onto the solid support in a pattern*; and 2) that the peptides be bonded to the solid support through a terminal amino acid.

Knichel discloses a composition comprising glass with gold electrodes patterned thereon. A SAM of thiol-modified peptides adheres to the entire gold surface. However, the SAMs in Knichel do not form a pattern on the gold. Rather, the gold forms a pattern on the underlying glass layer. The peptides in the composition of Knichel are not bound to the glass, but rather to the gold on top of the glass. Because Claim 1 requires the peptides to be bound to the solid support, the underlying glass layer therefore *cannot* be a "solid support" within the meaning of Claims 1-4 and 8-10. Only the gold surface, to which the peptide SAM is bonded, can be a "solid support, as the term is used in these claims. The peptides in Knichel cover the *entire* gold surface and therefore does not form a pattern on the solid support, as required by Claims 1-4 and 8-10. Therefore, the subject matter of Claims 1-4 and 8-10 is novel in view of Knichel.

C

Rejection of Claims 12 and 16 Under 35 U.S.C. § 102(a) or in the Alternative Under 35 U.S.C. §103(a) Over Duschl

The Examiner stated that Duschl teaches peptide self-assembled monolayers bound in a predetermined pattern having ordered areas where the peptides are and are not bound. The Examiner stated further that the patterns are formed by linear peptides containing a terminal cysteine group and are directly bound to the gold by the interaction of the thiol sidechain with the surfaces. The peptides have the structure $CY(NANP)_3$, with C being the terminal reactive group, Y the central linker and $(NANP)_3$. The Examiner reasoned that if the terminology "about 2" in Claims 12 and 16 include "1", then Duschl anticipates the subject of Claims 12 and 16; if "about 2" does not include "1", then the Examiner reasoned that it would have been obvious to modify the peptides of Duschl to have a longer linking group.

Applicants respectfully disagree with the Examiner that the patterned SAM disclosed by Duschl in "pre-determined". The SAMs in Duschl are formed by the following procedure:

> A mixture of palmitic acid and a thiolipid that is been spread on a water/air interface of a Langmuir trough to form a monolayer. This monolayer phase-separates on compression to give regularly distributed domains containing predominantly fatty acid. The size of the domains depends only on the self-organizing properties of the mixture and its manipulation on the water surface. The film is then transferred to a gold substrate where the thiolipids bind covalently to the support. The fatty acid is only physiosorbed to the gold surface and can be washed away. . . (paragraph bridging pages 1229-30).

Thus, the palmitic acid molecules, which have the hydrophilic carboxylic acid end group, associate and thereby separate from the hydrophobic thiolipids. As a result, the palmitic acid molecules and the thiolipid molecules each form their own domains at the air water interface. However, the number of domains formed and number of molecules which associate in each domain is unpredictable. Therefore, the pattern which forms from this process is random, unpredictable and irreproducible and therefore cannot be "pre-determined".

In contrast with Duschl, Claims 12 and 16 require the SAM pattern to be "pre-determined". To more clearly define the invention, the claims have been amended so that the pattern is "printed". As discussed in an earlier section of this response, a "printed pattern" has the

meaning commonly associated with the term, namely that the pattern has been offset from an image from another substrate. Therefore, the pattern can be predictably reproduced.

It is noted that Duschl provides no guidance on how to prepare SAMs of proteins in a printed, i.e., reproducible pattern. Therefore, the subject matter of Claims 12 and 16 is novel and non-obvious in view of Duschl.

Rejection of Claim 4 Under 35 U.S.C. § 103(a) in View of Duschl or Lopez, Further in View of Kumar *et al.* (U.S. Patent No. 5,512,131)

The Examiner stated that Duschl and Lopez teach patterned SAMs of peptides on gold, but neither teach making SAMs directly on glass substrates. The Examiner stated further that Kumar *et al.* (hereinafter "Kumar") discloses a method of patterning SAMs that is identical to that of the instant invention and that "a wide variety of materials and SAM-forming molecular species are suitable", listing glass and silica as some of the preferred materials. Therefore, the Examiner concluded that it would have been obvious to make the patterned monolayers of Duschl or Lopez on glass, as taught by Kumar.

A. Applicants' Invention

Applicants' invention solves the problem of binding *cells* to a peptide SAM that has a pre-determined pattern *and* affinity for specific proteins in the membranes of the cells. Thus, Applicants' SAMs have the important advantage of being able to select cells of a certain type and bind them in a desired pre-determined pattern. There are many advantages to binding cells in a pre-determined pattern, as opposed to binding them in random patterns. Examples of such advantages are disclosed in the paragraphs bridging pages 20-21 and 21-22 of the subject application:

> The invention permits very accurate control of cell population and density. The invention can be utilized to study cell growth and cellular interactions to external stimuli, including other cells, growth factors, repellants and inhibitors. Thus, the invention represents a significant advance in the ability to conduct research in biology and medicine.

> The understanding of complex neuronal connections is central to our comprehension of central nervous system function, and advances in doing so will benefit from combining engineering with molecular cell biology to analyze neuronal behavior under well-characterized and controlled conditions. Neurite outgrowth, guidance and connections can be studied on surfaces patterned with self-assembling peptides that contain cell-adhesion motifs. Controlling neurite outgrowth, including distances, angles and direction, can be important in controlling and studying synapse formation between neuronal cells guided into proximity. Neuronal cells attached to the described SAMs can be employed in the study of neuronal cell culture, synapse formation, neuronal connection engineering, screening neuropeptides, as well as pharmaceutical agents that stimulate, inhibit or alter the nature of nerve growth, and inter-connections.

Applicants solved this problem by utilizing a printed SAM formed from peptides that are bound to the solid support at one of the terminus of the peptides. In addition, the peptides have a ligand at the other terminus with a particular motif that binds specific proteins. As a result, cells expressing those proteins in the cell membrane are bound to the SAM in the desired pattern..

B. Duschl in view of Kumar

As discussed in the section of this Amendment that responded to the rejection under 35 U.S.C. § 102, Duschl teaches SAMs comprising peptides in a *random* pattern, i.e., a pattern that is not printed or pre-determined. Duschl also fails to teach that there would be any advantage in replacing randomly patterned peptide SAMs with a pre-determined, printed pattern.

Kumar discloses methods of microstamping a surface with a variety of chemical species to form a surface with a patterned SAMs. Kumar however, does not disclose or teach utilizing peptides with a cell binding motif to form the patterned SAM. Kumar also fails to teach that any advantage could be achieved by utilizing peptides of this type.

Duschl differs from the instant invention because the SAMs of the instant invention comprises peptides which are required to be in a *printed pattern*, i.e., a pattern that is reproducible and pre-determined. The instant invention is non-obvious over the combination of Duschl and Kumar because neither of these two reference provide the motivation to modify the *randomly* patterned peptide SAMs of Duschl to *printed, pre-determined* patterns of peptide

SAMs. It is well established in patent law that an obviousness rejection cannot be sustained unless the prior art provides motivation to modify what is disclosed so as to achieve the claimed invention:

> Although the Commissioner suggests that [the structure in the primary prior art reference] could readily be modified to form the [claimed] structure, '[t]he mere fact that the prior art could be so modified would have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Laskowski* 10 USPQ2d 1397 (Fed. Cir. 1989).

The instant invention is non-obvious over the combination of Duschl and Kumar because neither of these two reference suggest any advantage to replacing the ***randomly*** patterned peptide SAMs of Duschl with a ***printed, pre-determined*** patterns of peptide SAMs. As discussed in the section of this Amendment entitled "Applicants' Invention", Applicants' compositions, which comprise a peptide SAM printed in a pre-determined pattern on a surface, are an advance over the prior art in that these composition can bind specific cell types in a pre-determined pattern. As is also noted in the same section, the ability to bind specific cell types in a pre-defined pattern has many important advantages. Because Duschl and Kumar do not teach these advantages of a composition with a printed, pre-determined pattern of a peptide SAM and, in fact, fail to teach any other advantage of a composition of this type, the person of ordinary skill in the art would have no reason to modify the randomly patterned SAMs of Duschl so as to obtain the instant invention. The subject matter of Claim 4 is therefore non-obvious in view of Duschl and Kumar. Withdrawal of the rejection is requested.

C. Lopez in view of Kumar

As discussed in the section of this Amendment that responded to the rejection under 35 U.S.C. § 102, Lopez teaches absorbing protein onto non-peptide SAMs. Thus, in the compositions taught by Lopez do not comprise peptide SAMs. In addition, Lopez does not suggest any advantage in replacing a peptide SAM with a non-peptide SAM and therefore does not teach the desirability of making this modification. Kumar does not

overcome this shortcoming because there is no teaching or suggestion in Kumar of bonding the terminal amino acid of a peptide specifically and directly to a surface to form a same. Moreover, Kumar also does not teach the desirability of doing so. Therefore, the claimed invention is non-obvious in view of the combined teachings of Lopez and Kumar.

Rejection of Claims 7 and 12-16 Under 35 U.S.C. § 103 Over Duschl Further in View of Wang

The Examiner stated that Duschl teaches SAMs bound in a predetermined pattern having ordered areas where the peptides are and are not bound. She stated further that Duschl differs from the subject matter of Claims 7 and 12-16 only with respect to certain specifics of the central linker. The Examiner concluded that Wang provided the motivation to modify the SAMs disclosed in Duschl so as to achieve the invention of Claims 7 and 12-16.

As discussed in the section of this Amendment that responded to the rejection under 35 U.S.C. § 102, Duschl teaches SAMs comprising peptides in a *random* pattern, i.e., a pattern that is not printed or pre-determined. Duschl also fails to teach that there would be any advantage in replacing the randomly patterned peptide SAMs with a pre-determined, printed pattern.

Wang discloses compositions having SAMs with cell binding motifs. However, SAMs disclosed in Wang either are uniformly distributed over the entire surface (see the sentence bridging pages 21-22) or are *randomly* patterned (lines 79 of the last paragraph on page 19 and Figure 2). Wang discloses no advantage in modifying the uniformly distributed SAMs or the randomly patterned SAMs so as to form *printed, pre-determined* SAMs. In fact, Wang teaches only one utility for compositions comprising the SAMs disclosed therein, i.e., as a coating for stents to prevent thrombus formation of other intimal proliferation. Clearly, there would be no advantage in providing a stent coated with a SAM in a printed, pre-determined pattern.

Duschl differs from the instant invention because the SAMs of the instant invention comprises peptides which are required to be in a *printed pattern*, i.e., a pattern that is reproducible and pre-determined. The instant invention is non-obvious over the combination of Duschl and Wang because neither of these two reference provide the motivation to replace the *randomly* patterned peptide SAMs of Duschl with *printed, pre-determined* patterns of peptide SAMs. It is well established in patent law that an obviousness rejection cannot be sustained unless the prior art provides motivation to modify what is disclosed so as to achieve the claimed invention:

> Although the Commissioner suggests that [the structure in the primary prior art reference] could readily be modified to form the [claimed] structure, '[t]he mere fact that the prior art could be so modified would have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Laskowski* 10 USPQ2d 1397 (Fed. Cir. 1989).

Wang provides no motivation to modify the compositions disclosed by Duschl so as to achieve the claimed invention because Want fails to suggest any advantage to replace the *randomly* patterned peptide SAMs of Duschl with *printed, pre-determined* patterns of peptide SAMs. As discussed in the section of this Amendment entitled "Applicants' Invention", Applicants' compositions, which comprise a peptide SAM printed in a pre-determined pattern on a surface, are an advance over the prior art in that these composition can bind specific cell types in a pre-determined pattern. As is also noted in the same section of this Amendment,, the ability to bind specific cell types in a pre-defined pattern has many important advantages. Because Duschl and Kumar do not teach this advantage of printing a pre-determined pattern of a peptide SAM on a surface, and fail to teach any other advantage of a composition of this type, the person of ordinary skill in the art would have no reason, based on the teachings of Wang, to modify the randomly patterned SAMs of Duschl so as to obtain the instant invention. The subject matter of Claim 4 is therefore non-obvious in view of Duschl and Wang. Withdrawal of the rejection is requested.

Rejection of Claims 1-3, 6, 8-11 and 17 Under 35 U.S.C. § 103 Over Singhvi Further in View of Duschl

The Examiner stated that Singhvi teaches a method of patterning SAMs that is identical to that of the instant invention making "defined features" with "specific patterns" for placing cells in "predetermined". The Examiner stated further that Singhvi lacks a teaching of forming peptide monolayers directly by depositing a peptide in the non-printed regions. The Examiner reasoned that Duschl teaches patterned peptides directly bound to a gold substrate by the interaction of thiol sidechain with the surface. Therefore, the Examiner concluded Claims 1-3, 6, 8-11 and 17 were obvious over Singhvi in view of Duschl.

Singhvi teaches a method of forming SAM on a surface in a printed, pre-determined pattern to which cells can bind. However, the SAMs in Singhvi which bind cells are formed from alkanethiols; they are *not* formed from peptides which have binding motifs for particular proteins. Therefore, these SAMs therefore bind cells non-specifically and cannot be used to bind a particular cell type.

Applicants' compositions differ from the compositions disclosed in Singhvi because the SAMs in Applicants' composition are formed from peptides with particular motifs. Therefore, Applicants' composition can bind particular cell types specifically. In contrast, the compositions disclosed in Singhvi comprises SAMs formed from alkanethiols, which bind proteins non-specifically. The compositions therefore cannot distinguish between different cell types.

Duschl does not overcome the deficiencies of Singhvi as a prior art reference. Duschl discloses compositions comprising *randomly* patterned peptide SAMs. Moreover, Duschl does not provide any reason or benefit in replacing the random pattern with a printed, pre-determined pattern. In contrast, the peptide SAMs in Applicants' compositions are required to be in the form of a *printed pattern*, which means that they have a pre-determined shape that can be reproduced. As a result of the printed pattern and the binding motif on the peptides, Applicants' compositions represent an important improvement over the prior art because these compositions can both select certain cell types and bind them in a pre-defined, desired pattern. Duschl does not provide the motivation to replace the patterned alkanethiols in the SAM compositions of Singhvi with

peptides because Duschl does not suggest any benefit in producing a printed, pre-determined pattern of peptides.

Assuming *arguendo* that a suggestion was made in Singhvi or Duschl that a benefit could be achieved by replacing the alkanethiols in the SAMs of Singhvi with peptides, Applicants' invention is still non-obvious for a number of reasons. Firstly, there would not be a reasonable expectation of successfully preparing such compositions. Evidence in support of the position is provided in the Office Action itself. Applicants' note the following statement on page 4-5 of the Office Action:

> While self-assembled monolayers and even patterning of monolayers by stamping (referred to in the art as microcontact printing), were well known at the time of filing, there were only a few examples of different molecules used for patterning ("inking" the stamp) and to the examiner's knowledge, there were no examples at the time of filing of direct microcontact printing of peptides. The interaction of the "inking" compound and the stamp is crucial to the formation of good patterns, and is not predictable, as taught by Zhang. . .

Thus, even the Examiner acknowledged the unpredictability of replacing the alkanethiol in the compositions of Singhvi with a peptide. Secondly, even if the desirability of replacing the alkanethiol with a peptide had been suggested, there was still no reasonable expectation that the benefit could be achieved. For example, Applicants' compositions select certain cell types because the binding motifs in the peptide SAMs *specifically* bind to proteins that are selectively expressed in the membranes of the desired cell. The cells are then bound in a desired, pre-determined pattern. However, this result could not have been predicted solely on the basis of the teachings of Singhvi, which demonstrate *non-specific* binding of cells to SAMs, which comprise alkanethiols, and the teachings of Duschl, which suggest nothing about cell binding to SAMs.

For the reasons present above, it is respectfully submitted that the subject matter of Claims 1-3, 6, 8-11 and 17 is non-obvious over Singhvi in view of Duschl. Withdrawal of the rejection is requested.